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TITLE: Designer T Cells for Breast Cancer Therapy: Phase I Studies

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13. ABSTRACT ***(Maximum 200 Words)***

In the present report we describe studies using chimeric immune receptors consisting of an antibody fragment against the CEA tumor antigen joined to signaling portions of the T cell receptor(IgTCR). The antibody fragment confers CEA specificity to the receptor, while the signaling domains transmit T cell activation signals. These receptors allow the T cells (designer T cells) to bypass immune tolerance to CEA and to activate effector functions in a tumor specific manner. We have partially completed a phase I study using IgTCR-modified designer T cells. These studies demonstrate the specific signaling molecules activate specific T cell effector functions in a tumor specific manner. The study will be completed on a continuing no-cost extension with the funds allocated.

14. SUBJECT TERMS
breast cancer, chimeric immune receptors, CEA tumor antigen, T cells

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4. INTRODUCTION

Carcinoembryonic antigen (CEA) is a tumor-associated antigen which is expressed on ≈30-60% of metastatic breast tumors. The purpose of this research is to develop a new type of cancer therapy using autologous T cells modified with a chimeric immunoglobiin T cell receptor (IgTCR) directed against CEA + tumors. The specific objectives are to:

1. Complete setup for therapy.
2. Apply IgTCR-modified cells in a phase I clinical study in patients with metastatic CEA + breast tumors

In addition, to the above we have also carried out basic research efforts to create second-generation reagents that will enhance the therapy for future phase II/III studies.

5. BODY

The following activities were undertaken under the current year no-cost extension to the above referenced grant. It is noted that only two years of funding were provided by the DOD, whereas the task list was stated for the entire 4 year requested funding period. Accordingly, certain of the tasks were abandoned due to lack of funding, as indicated below.

I. Lab and clinical set up for therapy.

This was previously reported as completed.

However, we were previously mandated to redo this step by our local institution (not by the FDA), with a patient-dedicated facility. This was previously in a shared-use facility according that was acceptable under FDA specifications. We hired new staff during the past year and did retraining to re-establish this facility. Although we passed an outside inspector's certification, the institution still would not allow use of this facility. Hence, we have transferred production to the Cell Manipulation Core of the Dana Farber/Harvard Cancer Center. We are now in final stages of certification there.

II. Phase I clinical trial

This was trial was partially completed but interrupted due to reasons mentioned in the prior report. In the past year, we have responded to requests for redesign of the Cell Transduction Facility (CTF) for patient sample preparation. We have also established a DSMB to conduct patient monitoring on this gene therapy study. With various other administrative responses and design changes (only very modest changes to the treatment protocol), we expect to be ready to resume the study in 9/2002 and should complete the trial within the coming year. There remain 5 patients to treat on the phase I study.

All patient care funds have been preserved, and will be applied to complete the phase I tests.

III. Phase II study

Funding was not provided to support this study. This task is abandoned.

IV. Phase II study +IL2

Funding was not provided to support this study. This task is abandoned.

V. Laboratory studies for therapy improvement.

A. Prepare improved VPCs.

Completed in prior report.

B. Prepare improved helper cell lines.

Funding was not provided to support this effort. This task is abandoned.

C. Prepare CEA-IgG chimeric protein.

This product was completed in this recent year. Protein has been expressed. Biologic tests are to follow.

6. KEY RESEARCH ACCOMPLISHMENTS

- Technology transfer for cell production to Cell Manipulation Core
- New staff hiring and training.
- Protocol and consent modifications.
- Patient Treatment objectives deferred. To be accomplished with remaining funds.
- Preparation of CEA-IgG construct.

7. REPORTABLE OUTCOMES

- Publications:

  Ma QZ, Gonzalo-Danganzo R, Junghans RP. Genetically engineered T cells as adoptive immunotherapy of cancer. In Harrison P (ed) Cancer Chemotherapy & Biological Response Modifiers – Annual 20 Oxford: Elsevier Science. 2001:319-345.

8. CONCLUSIONS

The key clinical efforts of this study are deferred and will be completed in the coming year with conserved Department of Defense funds under this no-cost extension.

Note:
Extension not yet approved due to human use problems.

9. REFERENCES

None.

10. APPENDICES

A. Manuscripts

Ma QZ, Gonzalo-Danganzo R, Junghans RP. Genetically engineered T cells as adoptive immunotherapy of cancer. In Harrison P (ed) Cancer Chemotherapy & Biological Response Modifiers – Annual 20 Oxford: Elsevier Science. 2001:319-345.

Note:
Copy of manuscript not attached.